see original article on page 754

Is the renal risk of adults determined *in utero*?

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Renal (and cardiovascular) risks are to a considerable extent determined *in utero*. The results of the prospective study of Verburg *et al.*, sequentially measuring the growth of fetuses and the volume of their kidneys in a large population-based sample, identify some determinants of impaired growth of fetal kidneys.

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One of the more exciting recent epidemiological findings is the documentation that cardiovascular and renal risks in adult life are to a considerable extent determined in the prenatal and perinatal periods. This insight goes back to the observation of Barker[1,2] that, in adult life, subjects born with low birth weights have a higher risk of developing hypertension, metabolic syndrome, diabetes, and cardiovascular events. Although this hypothesis was criticized and initially not confirmed by all investigators, the evidence today appears to be quite solid.[3] It is currently not perfectly clear to what extent the higher cardiovascular risk in adult life is the result of retarded prenatal growth or of postnatal catch-up growth.[4] Because hypertension, metabolic syndrome, and type 2 diabetes are established risk factors for kidney disease, this alone would justify an interest of nephrologists in prenatal programming. Several years ago, however, the issue was carried even one step further by Brenner *et al.*, who postulated that compromised growth *in utero* per se leads to the development of fewer nephrons ('nephron underdosing'), thus causing hypertension and predisposition to renal disease in adult life.[5] It has meanwhile been confirmed that, at least among white subjects, hypertensive adults have a lower number of nephrons than normotensive adults.[6] Furthermore, experimental studies suggest that nephron underdosing may cause proteinuria and histological lesions of the kidney.

What are the insults that impair fetal organ growth, and by which mechanisms does nature then retard development of organs such as the pancreatic islets or kidney in response to an insult? Known insults include, for instance, malnutrition of the mother, uterine underperfusion, smoking, and hyperglycemia of the mother. A plausible mechanistic theory postulates that in order to guarantee optimal growth of the brain in the presence of restricted resources for growth, nature falls back on resources for the development of 'peripheral organs.' In the Babylonian Talmud it is stated that "the human body was given ten organs of which it is the task of the kidney to provide the human body with thought." To the chagrin of nephrologists, nature is apparently less wise than the ancient rabbis and does not share their high opinion of the kidney; if brain development requires support, the kidney is relegated to an organ of secondary importance.

Which mechanisms are used to guarantee preferential growth of the brain? Suspected mechanisms include diversion of metabolic substrates and of stem cells, as well as epigenetic changes — for example, methylation of DNA and acetylation of histones, alteration of homeostatic set points that control metabolism, and so on ('thrifty phenotype').

Is there evidence in humans that renal malfunction and chronic kidney disease are associated with and caused by retarded fetal growth and presumed nephron underdosing? The evidence is extremely sparse. One suggestive piece of evidence is the observation that in offspring of Dutch mothers who in the course of war events had been exposed during pregnancy to a devastating famine ('hunger winter'), a trend for higher urine albumin–creatinine ratios was found.[7] Furthermore, children with low birth weight had higher albumin excretion rates at age 19 years.[8] But a lower number of nephrons (first hit) in and by itself is presumably not sufficient to cause progressive chronic kidney disease. It is thought, however, to increase the risk of progressive chronic kidney disease if the kidney is injured by some insult (second hit), for example, hyperglycemia or immune disorder.

Against this background, information on the development of the human kidney from the prospective study of Verburg *et al.*[9] (this issue), with sequential measurements in a representative sample of the population to allow broader generalization, is of considerable interest. The authors extended previous findings that growth-restricted fetuses had smaller kidneys.[10] Verburg *et al.*[9] studied fetal growth characteristics and blood flow parameters using ultrasound and Doppler techniques to address the major determinants of fetal kidney growth among the following factors: maternal characteristics, fetal growth in the midtrimester and last trimester, fetal blood flow distribution between brain and kidney, and placental perfusion. The major readouts were kidney volume — this is, of course, an indirect index of nephron numbers at best, but

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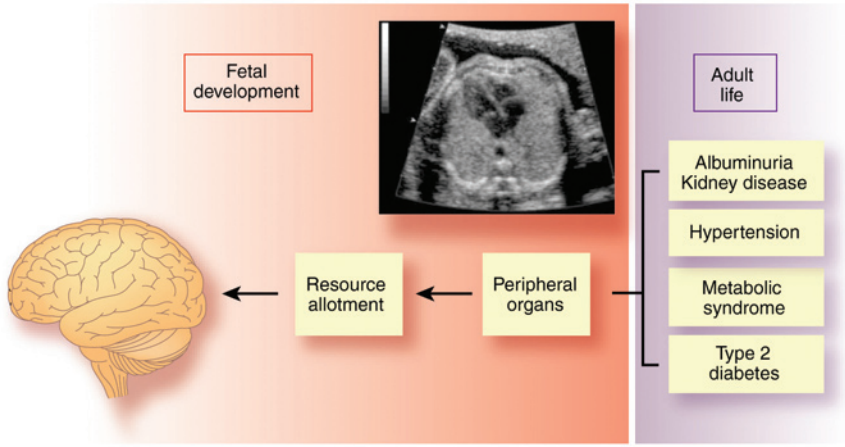

Figure 1 | Intrauterine programming and adult cardiovascular risk.

of interest in and by itself — and amniotic fluid volume as an indirect index of kidney function. The results are in part self-evident, in part valuable additions to our current state of knowledge (or ignorance).

To start with the negative findings, maternal smoking, obesity, blood pressure, and diabetes did not affect the readouts. With appropriate adjustments, fetal growth characteristics in the late trimester did affect fetal kidney volume, indicating that the late trimester is the decisive determinant for the achieved kidney volume. The mechanistically most interesting finding is the dependence of achieved fetal kidney volume on placental resistance and blood flow redistribution in favor of the brain — in accordance with the above-mentioned hypothesis that resources for growth of the brain take precedence over growth of the kidney — although further work is necessary to make sure that the associations found are causal.

As a side observation, the authors found that kidney volume was positively associated with amniotic fluid index and single deepest pocket. If confirmed, this may turn out to become a clinically valuable index and possibly an indirect index of nephron number.

The work-up used in the study by Verburg *et al.*[9] is certainly not clinically routine, but in principle such procedures may become valuable to recognize pregnancies at high risk and predict the need for follow-up.

Of great interest in the study cohort will be the evolution of blood pressure, urine findings (albuminuria), and indices of renal function in the ongoing follow-up of the offspring that had been evaluated as fetuses *in utero*. This will allow testing of the hypothesis that low fetal kidney volume translates into high cardiovascular and renal risk in adolescent and adult life (**see figure**).

One negative surprise of the study is the inability to confirm an impact on fetal kidney volume in two known high-risk pregnancy constellations, smoking and hyperglycemia. This may be a negative chance finding or may be due to limitations in the sensitivity of the method, or else fetal kidney volume may not faithfully reflect changes in kidney structure — for example, nephron underdosing. Admittedly it is also conceivable that the finding is correct, indicating that the impact on fetal kidney volume is not identical for all high-risk constellations. At any rate, further dedicated studies of such high-risk pregnancies would be desirable.

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